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ORIGINAL REPORT

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

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ABSTRACT

Purpose
To provide a more precise estimate of long-term survival observed for ipilimumab-treated patients with advanced melanoma, we performed a pooled analysis of overall survival (OS) data from multiple studies.

Methods
The primary analysis pooled OS data for 1,861 patients from 10 prospective and two retrospective studies of ipilimumab, including two phase III trials. Patients were previously treated (n = 1,257) or treatment naive (n = 604), and the majority of patients received ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706). We also conducted a secondary analysis of OS data (n = 4,846) with an additional 2,985 patients from an expanded access program. OS rates were estimated using the Kaplan-Meier method.

Results
Among 1,861 patients, median OS was 11.4 months (95% CI, 10.7 to 12.1 months), which included 254 patients with at least 3 years of survival follow-up. The survival curve began to plateau around year 3, with follow-up of up to 10 years. Three-year survival rates were 22%, 26%, and 20% for all patients, treatment-naive patients, and previously treated patients, respectively. Including data from the expanded access program, median OS was 9.5 months (95% CI, 9.0 to 10.0 months), with a plateau at 21% in the survival curve beginning around year 3.

Conclusion
To our knowledge, this is the largest analysis of OS to date for ipilimumab-treated patients with advanced melanoma. We observed a plateau in the survival curve, beginning at approximately 3 years, which was independent of prior therapy or ipilimumab dose. These data add to the evidence supporting the durability of long-term survival in ipilimumab-treated patients with advanced melanoma.

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INTRODUCTION

Melanoma that has progressed to American Joint Committee on Cancer stage IV remains an incurable disease with limited treatment options.[1] Historically, median overall survival (OS) was approximately 8 to 10 months with approved therapies for stage IV melanoma, and the 5-year survival rate from diagnosis was approximately 10%.[1] Few patients experienced durable clinical benefit with therapies approved before 2011, which either have not demonstrated an improvement in OS in a randomized, controlled phase III trial or, in the case of high-dose interleukin-2 (IL-2), have not been evaluated in a randomized, controlled phase III trial.[1] High-dose IL-2 was the first approved immunotherapy for stage IV melanoma in the United States based on a meta-analysis of phase II clinical trial data.[2] Of 270 patients from eight clinical trials, 17 (6%) had complete responses with a median duration of at least 59 months; at a median follow-up time of more than 7 years, disease progression had not occurred in any patient who responded for more than 30 months.[2] As a result of the potential for severe toxicities, treatment with high-dose IL-2 is limited to a carefully selected group of the healthiest patients.

Two new therapies were approved in 2011 for the treatment of unresectable or metastatic melanoma based on improvement in OS in randomized, controlled phase III trials.[3] Vemurafenib, a BRAF kinase inhibitor, was approved for the treatment of unresectable or metastatic melanoma harboring a *BRAF* V600 mutation.[3] The other approved agent was ipilimumab, a fully human immunoglobulin G_1 monoclonal antibody that was designed to block cytotoxic T-lymphocyte antigen-4 to augment antitumor T-cell immunity.[4,5] Ipilimumab, either alone at 3 mg/kg in previously treated patients or at 10 mg/kg in combination with dacarbazine in treatment-naive patients, improved OS while exhibiting a manageable safety profile in two randomized controlled phase III trials of unresectable stage III or stage IV (advanced) melanoma.[6,7] A proportion of ipilimumab-treated patients in phase II and III clinical trials of advanced melanoma has experienced long-term survival of at least 5 years.[8-10] In these trials, a consistent observation was that the survival curves seemed to reach a plateau between 2 and 3 years, suggesting that a proportion of the patients experienced a durable survival benefit. To provide a more precise estimate of long-term survival observed with ipilimumab therapy, we conducted a pooled analysis of OS data across multiple studies in advanced melanoma.

METHODS

Clinical Trials

The criteria for selection of the clinical studies that contributed data to these analyses were as follows: all studies in which OS data were available (either as primary, secondary, or exploratory end points) with updated survival data beyond 2008 and studies that included ipilimumab administration every 3 weeks for four doses at a minimum. Of 20 ipilimumab studies in advanced melanoma, eight were excluded (six phase I and two phase II studies) because they did not collect OS data and/or because they had a different initial treatment schedule than that of every 3 weeks for four doses (Appendix Table A1, online only).

Ten prospective and two retrospective studies of ipilimumab in advanced melanoma met the criteria for inclusion in the primary analysis (Table 1). These included seven clinical trials sponsored by Bristol-Myers Squibb (Wallingford, CT; two phase III [n = 790] and five phase II [n = 641]), three phase I/II trials conducted at the US National Cancer Institute (NCI; n = 180), and two observational studies sponsored by Bristol-Myers Squibb (n = 250). OS was prospectively evaluated in both phase III trials,[6,7] in all phase II trials,[11-15] and in the three phase I/II studies.[8] A primary objective of the observational studies was to evaluate OS from initiation of ipilimumab therapy.[16,17]

Detailed descriptions of the 10 prospective studies have been reported previously.[6-8,11-15] Briefly, the phase III trial MDX010-20 evaluated ipilimumab 3 mg/kg with or without the melanoma peptide vaccine gp100 versus gp100 alone in previously treated patients,[6] and the phase III trial CA184-024 evaluated ipilimumab 10 mg/kg plus dacarbazine versus placebo plus dacarbazine in treatment-naive patients.[7] In previously treated and treatment-naive patients, the phase II study CA184-004 investigated potential biomarkers of ipilimumab at 3 or 10 mg/kg,[11] and the phase II study CA184-007 evaluated the rate of ≥ grade 2 diarrhea with ipilimumab 10 mg/kg plus either prophylactic oral budesonide or placebo.[12] The phase II study CA184-008 evaluated ipilimumab 10 mg/kg in previously treated patients[13]; and CA184-022 was a phase II dose-ranging study of ipilimumab at 0.3, 3, or 10 mg/kg in patients who were intolerant to or who experienced progression on prior therapy.[14] In

Table 1. Summary of Ipilimumab Studies Included in Pooled OS Analyses

Study Identification No.	Reference	Trial Identifier	Phase	No. of Patients	Study Population	Ipilimumab Dose	Retreatment or Maintenance	Primary End Point
MDX010-20	Hodi et al[6]	NCT00094653	III	540	Previously treated	3 mg/kg ± gp100	Retreatment	OS
CA184-024	Robert et al[7]	NCT00324155	III	250	Treatment naive	10 mg/kg + dacarbazine	Maintenance	OS
CA184-022	Wolchok et al[14]	NCT00289640	II	217	Previously treated	0.3, 3, or 10 mg/kg	Maintenance	Best overall response rate
CA184-008	O'Day et al[13]	NCT00289627	II	155	Previously treated	10 mg/kg	Maintenance	Best overall response rate
CA184-007	Weber et al[12]	NCT00135408	II	115	Treatment naive or previously treated	10 mg/kg ± budesonide	Maintenance	Rate of ≥ grade 2 diarrhea
CA184-004	Hamid et al[11]	NCT00261365	II	82	Treatment naive or previously treated	3 or 10 mg/kg	Maintenance	Biomarkers of response and/or toxicity
CA184-042	Margolin et al[15]	NCT00623766	II	72	Melanoma with brain metastases	10 mg/kg	Maintenance	Disease control rate
NCI04C0083	Prieto et al[8]	NCT00077532	I/II	88	Previously treated	3, 5, or 9 mg/kg ± gp100	Not included	Objective response
NCI02C0106	Prieto et al[8]	NCT00032045	I/II	56	Previously treated	3 mg/kg + gp100 3 → 1 mg/kg + gp100	Not included	Objective response, safety
NCI03C0109	Prieto et al[8]	NCT00058279	I/II	36	Previously treated	0.1, 0.3, 1, 2, or 3 mg/kg + IL-2	Not included	Maximum-tolerated dose, objective response, pharmacokinetics, safety
CA184-338	Margolin et al[17]		Observational	160	Treatment naive	3 mg/kg	No	OS
CA184-332	Patt et al[16]		Observational	90	Treatment naive	3 mg/kg	No	OS
CA184-045	Hamid et al[18]	NCT00495066	US expanded access program	2,985	Previously treated	3 or 10 mg/kg	Maintenance only for patients treated at 10 mg/kg	NA

Abbreviations: IL-2, interleukin-2; NA, not applicable; OS, overall survival.

the CA184-042 study,[15] patients with melanoma with either asymptomatic or symptomatic brain metastases received ipilimumab 10 mg/kg. The three phase I/II trials evaluated ipilimumab with or without gp100 peptides or ipilimumab in combination with high-dose IL-2.[8]

The final data sets included in the primary analysis were from two ongoing observational studies of ipilimumab 3 mg/kg as a first-line therapy for metastatic melanoma (Table 1).[16,17] The first (CA184-332) is a community-based assessment of ipilimumab in which patients (n = 90) were retrospectively identified from US oncology practices using an electronic medical record system and medical record abstraction.[16] This study evaluated patient baseline characteristics and OS. The second study (CA184-338) involved a US multisite observational medical record review that evaluated patient baseline characteristics, safety, and OS data (n = 160).[17]

An additional analysis of OS was conducted that included OS data from 2,985 patients enrolled onto a US multicenter, open-label, expanded access treatment protocol (EAP; CA184-045). Patients initially received ipilimumab 10 mg/kg in the EAP; however, the protocol was amended in March 2010 to administer ipilimumab 3 mg/kg.[18] The protocol was further amended in March 2011 to include retrospective collection of OS in patients who had received ipilimumab 3 or 10 mg/kg.[18]

Data Analyses

In the primary analysis, individual patient OS data were pooled from the 12 ipilimumab studies described in the previous section. EAP data were excluded from the primary analysis because of the incomplete collection of OS data but were combined with the primary analysis cohort to assess the sensitivity of the primary analysis. Eight of the 12 studies in the primary analysis (including those from the NCI) had more than 5 years of minimum follow-up, defined as the duration between the time when the last patient was either treated or randomly assigned until the time of analysis.

Patients were observed for OS for up to 10 years in some studies (ie, the three NCI trials). OS was defined as the time from random assignment or first dosing date until death, with censoring on the last known alive date. Nonrandomized subset analyses of OS were conducted by prior treatment status regardless of dose, and by dose regardless of prior treatment status. Median estimates with 95% CIs were computed using the Brookmeyer and Crowley method, as in prior ipilimumab trials.[6,7] OS rates at 3 years were estimated from the Kaplan-Meier survival probability along with its CI, obtained using log cumulative hazard transformation.

To assess the poolability of data from different ipilimumab studies with varying lengths of survival follow-up, a rank test of homogeneity among all 12 studies included in the primary analysis was conducted, along with an evaluation of a Cox proportional hazards model with study and pretreatment status as predictors. Two sensitivity analyses were used to assess the impact of early patient censoring on 3-year survival rates. The first was conducted on four studies, with a total of 1,040 patients, in which OS was the primary end point (MDX010-20, CA184-024, CA184-332, and CA184-338). The second was conducted on 10 of the 12 studies (excluding only MDX010-20 and CA184-042), with 1,249 patients, in which OS follow-up continued until the time of the current analysis.

RESULTS

One thousand eight hundred sixty-one patients with advanced melanoma who received ipilimumab in clinical studies were included in the primary analysis of OS (Table 1). Before receiving ipilimumab, approximately two thirds of the patients (n = 1,257) had been previously treated for advanced disease. The majority had received ipilimumab at the approved dose of 3 mg/kg (n = 965) or at the investigational dose of 10 mg/kg (n = 706); the remaining 190 patients received other doses and were included for completeness, given that the studies met the specified inclusion criteria for the present analysis.

Ipilimumab was given at least every 3 weeks for up to four doses (induction phase). In some studies (Table 1), eligible patients who achieved either a confirmed objective response or stable disease of ≥ 3 months and did not experience progression could also receive ipilimumab maintenance therapy (every 12 weeks beginning at week 24). Some patients in the phase II and III studies were re-treated with ipilimumab (every 3 weeks for four doses) on disease progression, provided that they had achieved an objective response or prolonged stable disease from the first course of treatment.

The primary analysis of 1,861 patients demonstrated a median OS of 11.4 months (95% CI, 10.7 to 12.1 months), with a 3-year survival rate estimated to be 22% (95% CI, 20% to 24%). Median follow-up time was approximately 11 months; 10% of the patients were observed for at least 50 months, with a maximum follow-up time of 119 months. Across studies, durations of median follow-up were in the range of 9 to 15 months, with the exception of the phase II study CA184-042 (involving patients with brain metastasis), for which the median follow-up time was 5.4 months. A rank test of homogeneity and a Cox proportional hazards model with study and pretreatment status as predictors showed a statistically significant difference between the 12 studies, of which three (CA184-007, CA184-042, and CA184-338) were identified as outliers. After excluding these three studies, the rank test demonstrated homogeneity among the remaining studies, and the result from a Cox proportional hazards model also confirmed that study is no longer a strong predictor ($P > .14$) for OS. The 3-year OS rate was 20.3% (95% CI, 18.1% to 22.5%) in this analysis, demonstrating a consistent result that supports the reliability of the pooled analysis including data from all 12 studies.

The primary analysis included 254 patients who were still alive at least 3 years after receiving their first dose of ipilimumab. Median follow-up time for the 254 patients was 69 months (interquartile range, 49 to 78 months), with the longest survival follow-up for an individual patient of 9.9 years. The Kaplan-Meier OS curve showed that a plateau began around year 3 and extended up to year 10 in some patients (Fig 1). Censoring among patients for each study is shown in Table 2. The results of sensitivity analyses showed no major impact of censoring on the 3-year OS rates, with results consistent to those of the pooled analysis in all 12 studies (3-year OS including only the four

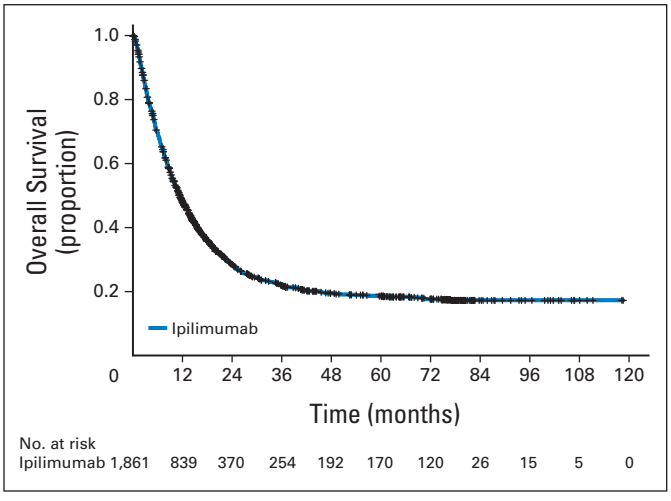

Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

Table 2. Summary of the Number of Censored Events in Ipilimumab Studies

Study Identification No.	No. of Patients	Censored Events	
		No.	%
MDX010-20	540	134	24.8
CA184-024	250	51	20.4
CA184-022	217	42	19.4
CA184-008	155	35	22.6
CA184-007	115	43	37.4
CA184-004	82	16	19.5
CA184-042	72	15	20.8
NCI04C0083	88	18	20.4
NCI02C0106	56	7	12.5
NCI03C0109	36	8	22.2
CA184-338	160	76	47.5
CA184-332	90	42	46.7

studies with OS as the primary end point, 20.2%; 95% CI, 17.2% to 23.2%; and 3-year OS including only studies in which OS follow-up continued to the time of the current analysis, 23.7%; 95% CI, 21.1% to 26.3%).

When survival data were analyzed by prior therapy (Fig 2), median OS was 13.5 months (95% CI, 11.9 to 15.4 months) for treatment-naive patients and 10.7 months (95% CI, 9.6 to 11.4 months) for previously treated patients, with 3-year survival rates of 26% (95% CI, 21% to 30%) and 20% (95% CI, 18% to 23%), respectively. In a subset analysis by ipilimumab dose (Fig 3), regardless of prior therapy, median OS was 11.4 months (95% CI, 10.3 to 12.5 months) for ipilimumab 3 mg/kg, 11.1 months (95% CI, 9.9 to 13.0 months) for ipilimumab 10 mg/kg, and 12.4 months (95% CI, 10.4 to 15.1 months) for other dosing regimens; the 3-year survival rates for these subgroups were 21% (95% CI, 17% to 24%), 24% (95% CI, 21% to 28%), and 20% (95% CI, 14% to 26%), respectively.

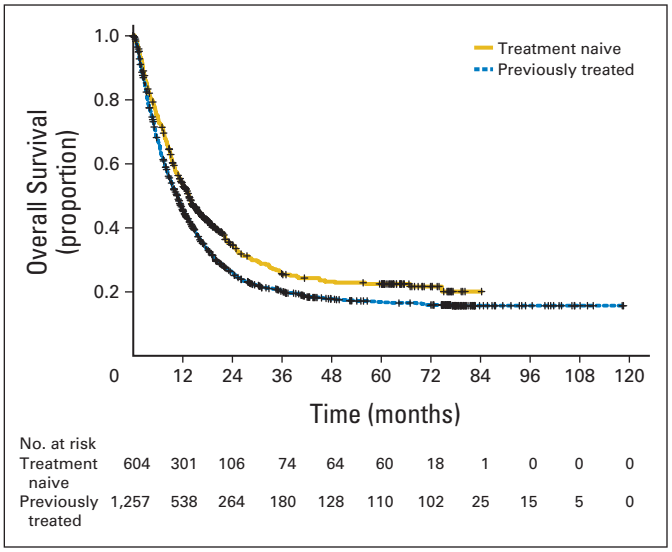

Fig 2. Subset analysis of overall survival (OS) by prior therapy. Nonrandomized subset analysis of OS in treatment-naive (n = 604) and previously treated (n = 1,257) patients with metastatic melanoma who received ipilimumab in 10 prospective trials and two retrospective, observational studies. Median OS was 13.5 months (95% CI, 11.9 to 15.4 months) for treatment-naive patients and 10.7 months (95% CI, 9.6 to 11.4 months) for previously treated patients, with 3-year survival rates of 26% (95% CI, 21% to 30%) and 20% (95% CI, 18% to 23%), respectively. Crosses indicate censored patients.

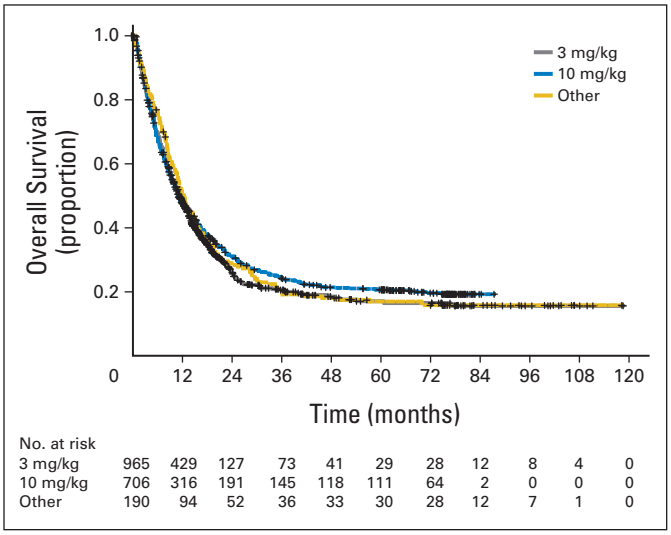

Fig 3. Subset analysis of overall survival (OS) by ipilimumab dose. Nonrandomized subset analysis of OS in patients who received ipilimumab at 3 mg/kg (n = 965), 10 mg/kg (n = 706), or other dosing regimens (n = 190) in 10 prospective trials and two retrospective, observational studies. Median OS was 11.4 months (95% CI, 10.3 to 12.5 months) for 3 mg/kg, 11.1 months (95% CI, 9.9 to 13.0 months) for 10 mg/kg, and 12.4 months (95% CI, 10.4 to 15.1 months) for other dosing regimens; the 3-year survival rates were 21% (95% CI, 17% to 24%), 24% (95% CI, 21% to 28%), and 20% (95% CI, 14% to 26%), respectively. Crosses indicate censored patients.

A secondary analysis was conducted that included the primary cohort and 2,985 patients from the EAP (total of 4,846 patients). The latter included patients with an Eastern Cooperative Oncology Group performance status of 2, patients with brain metastases, and patients with noncutaneous primary tumors (ocular or mucosal melanoma). Median OS was 9.5 months (95% CI, 9.0 to 10.0 months), with a 3-year survival rate of 21% (95% CI, 20% to 22%). As with the primary analysis, the Kaplan-Meier OS curve revealed a plateau beginning around year 3 that extended up to 10 years in some patients (Fig 4).

DISCUSSION

To our knowledge, this OS analysis is the largest to date in patients who received ipilimumab for advanced melanoma in clinical investigations or an EAP. Consistent with the results of prior individual studies of ipilimumab, Kaplan-Meier OS curves in the current analyses showed that a plateau seemed to begin around year 3. These results suggest that the majority of patients who reached this milestone time point had a low risk of death thereafter. Similar observations regarding a plateau in the OS curve have been made with IL-2 in advanced melanoma, although in a smaller proportion of patients.[19] The long-term survival of patients who have received immunotherapies has prompted some investigators to introduce the concept of curative potential.[19] Notably, the present analyses draw from data on survival status only and, thus, cannot be used to infer patients' status of disease (ie, whether

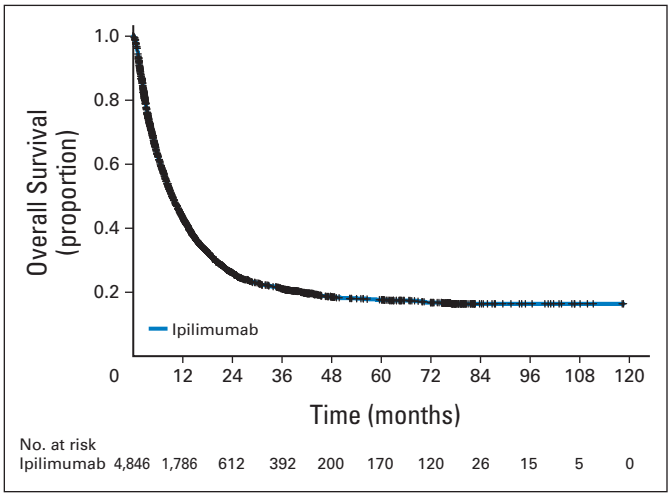

Fig 4. Pooled overall survival (OS) analysis with expanded access protocol (EAP) data. Individual patient survival data were pooled from 1,861 patients with metastatic melanoma from 12 clinical investigations of ipilimumab and 2,985 patients with metastatic melanoma from a US EAP (n = 4,846). Median OS was 9.5 months (95% CI, 9.0 to 10.0 months) with a 3-year survival rate of 21% (95% CI, 20% to 22%). Crosses indicate censored patients.

long-term survivors have residual tumor or are completely free from disease).[8]

We observed an apparent plateau in the survival curve regardless of prior therapy, ipilimumab dose, or treatment regimen. In all analyses, including those with OS data from patients in the EAP, the survival curves seemed to consistently begin to plateau around year 3 and extended up to 10 years in some patients. Although there were differences among studies with respect to length of follow-up, eight of the 12 studies (with approximately 1,000 patients) had more than 5 years of minimum follow-up time. Thus, although a limitation of the pooled OS analysis is the different follow-up times of the studies, the shape of the OS curve with an apparent plateau beginning at approximately 3 years is consistent with that observed in individual phase II and III studies of ipilimumab in advanced melanoma.[9,10]

Median OS and 3-year survival rate were higher for treatment-naive patients than for previously treated patients (13.5 and 10.7 months and 26% and 20%, respectively), but because these nonrandomized subgroup analyses did not account for key baseline prognostic factors, no definitive conclusion can be made regarding the relative treatment effects of ipilimumab in these populations. Similarly, the 3-year survival rate was numerically greater for the patient subgroup who received ipilimumab 10 mg/kg than for the subgroup who received ipilimumab 3 mg/kg. However, as for the analyses by prior therapy, these nonrandomized subgroup analyses do not permit definitive conclusions regarding potential survival differences between ipilimumab doses. An ongoing phase III trial (CA184-169) will prospectively compare OS between ipilimumab 3 and 10 mg/kg in patients with advanced melanoma.[20]

The primary analysis included patients with poor prognostic factors for OS in stage IV melanoma, such as elevated serum lactate dehydrogenase levels and brain metastases at baseline.[21] In both phase III trials of ipilimumab in advanced melanoma, more than one third of patients had elevated serum lactate dehydrogenase levels at baseline,[6,7] and five of the studies included patients who had asymptomatic/stable brain metastases at baseline (MDX010-20, CA184-007, C184-042, C184-332, and CA184-338). Moreover, patients in all 12 ipilimumab studies and the EAP were not selected for *BRAF* V600 mutation status. Median OS was lower when patients from the EAP were included in the analysis, which is not unexpected given that these patients generally had poorer prognostic factors. For example, patients with an Eastern Cooperative Oncology Group performance status of 2 were eligible for the EAP, whereas these patients were largely excluded from ipilimumab clinical trials. Further analyses are required to determine the specific disease characteristics of long-term survivors after ipilimumab therapy.

Among patients observed for survival in the NCI phase I/II trials, 15 patients had complete responses (six of whom had received ipilimumab and IL-2), and 18 patients had partial responses.[8] However, nine of the long-term survivors did not achieve a response. Similar observations have been made in other ipilimumab studies. Among 88 patients who survived at least 4 years in studies CA184-007, CA184-008, and CA184-022, 35 (40%) achieved an objective response, 29 (33%) had stable disease, and 22 (25%) had progressive disease.[22] In the phase III trial CA184-024, only 50% of the patients who received ipilimumab plus dacarbazine and were alive at least 5 years had an objective response.[10] In ipilimumab clinical trials, responses improved over time without further ipilimumab treatment; in others, stable disease improved to an objective response, and in some cases, patients with progressive disease achieved stable disease or an objective response over time.[6,23]

Limitations to the present analyses include the lack of a control group, the inclusion of multiple studies with different patient populations, and the fact that the studies were conducted in different eras, spanning a period of approximately 10 years. Although there were no other therapies that had definitively demonstrated improvements in OS at the time many of the patients were undergoing treatment, it is unclear from these analyses the extent to which treatments received after ipilimumab may have contributed to survival. Thus, it is possible that treatments received subsequent to ipilimumab may have contributed to OS in the analyzed population. Despite these limitations, the large numbers of patients and extent of follow-up (up to 10 years) render this analysis an important part of the ongoing evaluation of long-term survival that has been observed in a proportion of ipilimumab-treated patients with advanced melanoma.[8-10]

In conclusion, this pooled analysis of OS adds to the evidence supporting the durability of long-term survival in a proportion of ipilimumab-treated patients with advanced melanoma. We observed a median OS of 11.4 months and an apparent plateau in the OS curve around year 3, when survival rates ranged from 20% to 26%, with follow-up to 10 years in some patients. Considering the historic median OS of approximately 8 to 10 months and a 5-year survival rate of approximately 10% in advanced melanoma,[1] the results presented herein are encouraging for patients diagnosed with this aggressive disease. Future investigations will focus on approaches to increase the proportion of patients who experience long-term survival, including combination studies with other inhibitors of immune checkpoint pathways (eg, PD-1).[24]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a

financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Administrative support: Dirk Schadendorf, Debra Patt
Provision of study materials or patients: Dirk Schadendorf, Jeffrey S. Weber, Kim Margolin
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Appendix

Table A1. Ipilimumab Studies in Advanced Melanoma That Were Excluded From Pooled OS Analyses

Study Identification No. and Trial Identifier	Phase	Primary Objective	Secondary Objective(s)
MDXCTLA4-02	I	To determine if administration of ipilimumab causes nonspecific T-cell activation	Establish safety/tolerability profile for ipilimumab; determine the pharmacokinetic profile of ipilimumab; identify any preliminary evidence of efficacy; and to assess the development of a host immune response to ipilimumab
MDXCTLA4-04	I	Evaluate the safety and tolerability of CTLA4 blockade by MDX-010 when used in combination with Melacine vaccination	Evaluate the potential activity of this combination in the treatment of malignant melanoma
MDX010-03; NCT00025181	I	Establish a safety profile for repeated doses of ipilimumab combined with a peptide vaccine consisting of tyrosinase 368-376, gp100, and MART-1: 26-35 peptides emulsified with Montanide ISA 51	Determine if administration of the combination caused antigen-specific activation; determine the clearance profile of ipilimumab administered with the peptide vaccine; and assess the development of a host immune response to repeated doses of ipilimumab with the peptide vaccine
MDX010-15; NCT00729950	I	Determine the safety and pharmacokinetic profile of single and multiple doses of MDX-010 derived from a transfectoma or a hybridoma cell line	Determine the clinical activity of single and multiple doses of ipilimumab, determine the single-dose maximum-tolerated dose of ipilimumab, and determine the immunologic activity of ipilimumab
CA184-078; NCT00796991	I	Estimate the effect of ipilimumab on the pharmacokinetics of paclitaxel/carboplatin and dacarbazine and estimate the effect of paclitaxel/carboplatin and dacarbazine on the pharmacokinetics of ipilimumab in patients with treatment-naive advanced melanoma	
CA184-087; NCT00920907	I	Assess the pharmacokinetics of ipilimumab process C relative to ipilimumab process B administered by intravenous infusion in patients with advanced melanoma	
MDX010-08; NCT00050102	II	Determine the safety and activity profile of ipilimumab (3 mg/kg every 4 weeks for 4 doses) and determine whether the addition of dacarbazine would augment the effects of ipilimumab in patients with chemotherapy-naive metastatic melanoma with a tolerable toxicity profile	Determine the induction of tumor-directed immune responses based on tumor biopsies and determine the pharmacokinetic profile of multiple doses of ipilimumab alone or in combination with dacarbazine
MDX010-16; NCT00084656	II	The primary objective of the first part of the study was to achieve at least a 40% irAE rate defined by the induction of grade 1, grade 2, or acceptable grade 3 drug-related irAEs. The primary objectives of the second part of the study were to determine the time to disease relapse and to determine the rate of acceptable irAEs defined by the induction of grade 1, grade 2, or acceptable grade 3 drug-related irAEs	

Abbreviations: irAE, immune-related adverse event; OS, overall survival.